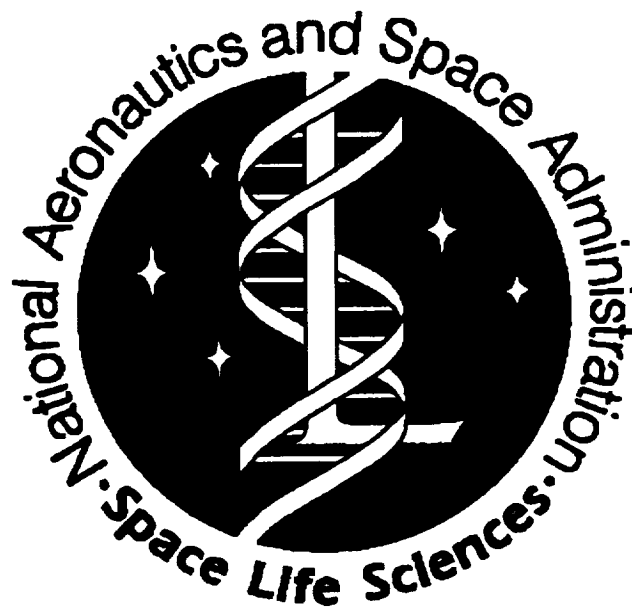


REGULATORY PHYSIOLOGY DISCIPLINE SCIENCE PLAN

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**SPACE PHYSIOLOGY AND COUNTERMEASURES PROGRAM
LIFE SCIENCES DIVISION
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Appendix 1

REGULATORY PHYSIOLOGY DISCIPLINE SCIENCE PLAN

1.0 INTRODUCTION

The focus of the Regulatory Physiology discipline of the Space Physiology and Countermeasures Program is twofold. First, to determine and study how microgravity and associated factors of space flight affect the regulatory mechanisms by which humans adapt and achieve homeostasis and thereby regulate their ability to respond to internal and external signals; and, second, to study selected physiological systems that have been demonstrated to be influenced by gravity. The Regulatory Physiology discipline, as defined here, is composed of seven subdisciplines: 1) Circadian Rhythms, 2) Endocrinology, 3) Fluid and Electrolyte Regulation, 4) Hematology, 5) Immunology, 6) Metabolism and Nutrition, and 7) Temperature Regulation.

1.1 PURPOSE

The purpose of this Discipline Science Plan is to provide a conceptual strategy for NASA's Life Sciences Division research and development activities in the area of regulatory physiology. It covers the research areas critical to NASA's programmatic requirements for the Extended-Duration Orbiter, Space Station Freedom, and exploration mission science activities. These science activities include ground-based and flight; basic, applied, and operational; and animal and human research and development. This document summarizes the current status of the program, outlines available knowledge, establishes goals and objectives, identifies science priorities, and defines critical questions in regulatory physiology. It contains a general plan that will be used by both NASA Headquarters Program Offices and the field centers to review and plan basic, applied, and operational intramural and extramural research and development activities in this area.

2.0 GOALS AND OBJECTIVES

2.1 GOALS

The long-range goals of the NASA Regulatory Physiology research program are to:

- Determine and understand the short- and long-term physiological adaptation(s) of humans to the space environment
- Evaluate the efficacy of physiological and performance countermeasures.

2.2 OBJECTIVES

The objectives of the subdisciplines of the NASA Regulatory Physiology research program are listed below:

- **Circadian Rhythms:** Describe and understand the effects of gravity and the space-flight environment on biological rhythms of various physiological systems
- **Endocrinology:** Understand the hormonal mechanisms that underlie the physiological responses to space flight
- **Fluid and Electrolyte Regulation:** Describe and understand the effects of space flight on renal function, fluid distribution, and electrolyte regulation in humans
- **Hematology:** Characterize the anemia that is present following space flight and determine the causes and mechanisms involved in the loss of red blood cell mass
- **Immunology:** Define and understand the changes in immunocompetency that occur in response to space flight
- **Metabolism and Nutrition:** Understand and describe changes in metabolism that occur in space flight and define how and to what extent nutritional requirements may be altered
- **Temperature Regulation:** Understand the effects of gravity and space flight on the regulation of body temperature and thermal comfort of the crew.

This plan incorporates recommendations from reports by the Committee on Space Biology and Medicine (Goldberg), the NASA Life Sciences Strategic Planning Study Committee (Robbins), and the Federation of American Societies for Experimental Biology (FASEB) (see 12.0, Selected References).

Current knowledge about physiological changes associated with short-term and long term space flight is summarized in Appendix 1, which is from Space Physiology and Medicine, 2nd. edition, by Drs. Nicogissian, Leach-Huntoon, and Pool.

3.0 CIRCADIAN RHYTHMS

3.1 INTRODUCTION

Circadian rhythms (i.e. characteristics of living systems that cycle with a relatively fixed and predictable period of about 24 hours) are a fundamental property of all eukaryotic organisms. Indeed, circadian rhythmic variations are observed in almost all biochemical, cellular, physiological, and behavioral systems.

It has been clearly established that these rhythms are generated by “internal (i.e. endogenous) biological clocks.” The circadian clock is normally entrained or synchronized to the 24-hour changes in the physical environment by external signals, such as the light-dark cycle. Extensive biochemical, molecular and cellular studies are ongoing to elucidate the biological mechanisms by which circadian rhythms are generated and entrained. Biological rhythms are a common feature of most, if not all, regulatory systems, and the proper timing of circadian rhythms is vital for the optimal health of the organism. Recent studies in humans have focused on the importance of circadian rhythms and sleep for normal mental and physical health, and how these functions can be influenced to optimize human performance. These studies emphasize the need for the proper scheduling of work-rest-sleep activities and design of lighting environments for ensuring optimal human performance.

A number of reports, from both within and outside of NASA, have emphasized the need to examine circadian rhythms in the space environment because the study of biological rhythms in space is important for the health and performance of space crews.

3.2 BACKGROUND AND CURRENT KNOWLEDGE

The fundamental question regarding circadian rhythms that was the focus of early NASA-sponsored research was, “Do circadian rhythms persist in the absence of environmental time cues (e.g. light or temperature changes) in outer space?” The answer to this question was important for addressing the issue of whether or not the clock that regulates 24-hour rhythms resides within the organism or within the Earth’s physical environment. The answer was clear: circadian rhythms persist outside of the Earth’s environment, and thus the clock(s) regulating circadian rhythms are within living organisms. Studies carried out on Spacelab in the fungus Neurospora crassa and in the unicellular green alga Chlamydomonas reinhardtii, have clearly demonstrated that circadian rhythms persist in space. Of great importance, however, is the finding that rhythms can show abnormal amplitudes and phase relationships to the light-dark cycle in space. Such abnormalities in biological rhythms have been observed in plants, rats, and monkeys studied on various U.S. and Soviet space missions. In addition, ground-based studies with animals have shown that exposure to hypergravity can also have disruptive effects on various circadian rhythms in mammals.

Few attempts have been made to study human circadian rhythms in space in any detailed fashion. While physiological data were recorded during isolated nights of sleep on three of the Skylab missions, rhythms in the sleep-wake cycle have not been monitored in space. In general, reasonably good sleep has been reported in space, although a number of abnormalities that relate to specific stages of sleep have been noted. Essentially, nothing is known about how other circadian rhythms are affected by the space environment. Of particular concern is how circadian patterns of various hormones and/or metabolic processes may be altered in reduced gravity.

3.3 CRITICAL QUESTIONS (In priority order)

1. What are the effects of the space environment on sleep, sleep cycles, or the generation, expression (period, phase, amplitude and/or waveform),

and entrainment of metabolic, endocrine, and/or behavioral circadian rhythms? Of these effects, which result from altered gravity and which result from other environmental factors?

2. What are the effects of intermittent and variable gravity fields on circadian rhythms, and how does this affect the use of artificial gravity as a countermeasure to microgravity? Can gravity be used as a potential synchronizing agent of circadian rhythms? What are the physiological mechanisms that mediate the effects of gravity on the biological clock?
3. What are the optimal environmental conditions for ensuring synchronization of circadian rhythms in space, and what are the most appropriate work-rest schedules for ensuring optimal health and performance?
4. What are the effects of space-induced alterations in circadian rhythms on human health and performance? What are the times for peak performance ~~during EVA?~~
5. What are the optimal conditions for synchronizing the circadian rhythms of mission control personnel to the mission schedules? How is performance of mission personnel affected by their various work-rest schedules?
6. What are the effects of exercise on circadian rhythms and sleep? What pharmacological and nonpharmacological (e.g. light, exercise) agents can be used to reset the human biological clock? What are the effects of routine administration of pharmacological agents in space on circadian rhythms and sleep?
7. What are the appropriate ground-based analogs for studying the effects of extreme environments on human circadian rhythms?
8. What are appropriate mathematical and computer models for simulating the effects of the space environment on circadian rhythms?
9. What are the effects of non-gravity-related physical-chemical and psychological space-flight-induced stressors on circadian rhythms and sleep?
10. What are the long-term effects of the space environment on the interaction between the circadian and reproductive systems?
11. What roles do age and gender play in the response of the circadian system to the space environment?
12. What are the effects of cephalad fluid shifts on circadian rhythms?

4.0 ENDOCRINOLOGY

4.1 INTRODUCTION

The transmission of all information in the body from one cell system to a more distant target depends almost entirely on neurohumoral, neuroendocrine, and endocrine communication systems. In recent years, endocrinology has changed from the study of a relatively few, circumscribed regulatory systems and metabolic effects to include more diffuse and extensive control mechanisms within and outside (e.g. kidney, gut) the central nervous system — often with widespread regulatory effects.

Hormones play an extensive modulatory role throughout the body. Endocrine and neuroendocrine secretions are the basis by which regulatory changes are developed and sustained. Knowledge of changing synthesis, release, and response during space flight is essential to our understanding of how the body adapts to this new environment. Of particular importance is the effect of hormones on the brain — not only in terms of homeostatic regulation of such parameters as body temperature, fluid balance, or biological rhythms — but also of behavior, emotional state, and performance. It, therefore, is central to the understanding of the role of gravity in the evolution and regulation of living systems, as well as of the induced physiological and behavioral changes that occur in humans in space, to understand the endocrine and metabolic processes involved in adapting to that environment.

The need to measure and investigate changes in endocrine regulatory systems was recognized from the start of the manned space program. At first, the primary interest was related to the ability of crews to withstand and respond to the stresses of space flight. Data from in-flight studies continually demonstrate that endocrine mechanisms underlie many of the major biomedical changes during space flight.

Recommendations by review and advisory committees have consistently emphasized the need to support experimentation to determine the endocrine mechanisms underlying the fluid, electrolyte, cardiovascular, musculoskeletal, immune, erythropoietic, and general metabolic responses to space flight.

Over the course of the manned space flight programs since 1965, a wide variety of endocrine hormone and related measurements have been made. In-flight measurements on Gemini VII, Skylab, and the more recent Shuttle flights have revealed clear and consistent patterns of change in many systems. Additionally, recent data from rat tissue obtained after COSMOS and Spacelab missions have suggested possible molecular mechanisms that might explain endocrine irregularities. These studies have contributed to the development of several effective countermeasures. Negative feedback effectiveness on CNS regulatory mechanisms may be reduced. Age and gender, as well as sleep, emotions, extravehicular activity (EVA), and the physical activity induced by workload should be considered along with prescribed medications and countermeasures in attempts to evaluate the effects of microgravity on endocrine systems. Implementation is also an important factor. For example, COSMOS data suggest that growth hormone concentrations (as assayed by radioimmunoassay) do not reflect biological activity. This may also be the case for ACTH and insulin.

4.2 BACKGROUND AND CURRENT KNOWLEDGE

Description of the response of the human endocrine system to space flight has come from comprehensive measurement of hormones in the blood and urine of crews before and after flight as well as during flight (Gemini, Apollo, Skylab, and STS). Data from animal flight experiments (SL-3, SLS-1, COSMOS) reflect pre- and postflight measurements only. Nevertheless, a broad spectrum of endocrine system responses to space flight have been measured in rats, including growth hormone and reproductive, calcium regulating, thyroid, and adrenocortical hormone changes.

Considerable evidence has accumulated to indicate that head-down bedrest provides an acceptable ground-based simulation of the effects of prolonged weightlessness. Nevertheless, there are differences in some of these effects and in the time course of the measured changes. Bedrest cannot provide zero gravity, though the effects of gravity in the Gz vector are greatly diminished. Furthermore, the motivation cannot begin to compare with actual flight. Space flight, on the other hand, does not merely provide weightlessness, but is a composite of operational conditions so that in addition to weightlessness, contributions to the overall results are made by the emotional and physical forces of liftoff; the debilitating symptoms of space sickness; and the isolation, workload, sleep and rhythm disturbances, and interactions with life support systems and medications. These differences must be considered in extrapolating endocrine data from ground-based studies to spaceflight and emphasize the need for in-flight confirmation of findings from ground-based studies. On the other hand, more in-depth investigation, particularly of mechanisms and of the value of countermeasures, can be done more simply, practically, accurately, and economically with bedrest studies.

Weightlessness and bedrest alike produce a characteristic headward redistribution of blood volume. This shift results in increased intrathoracic pressure, stimulation of cardiopulmonary receptors, and stimulation of aortic and carotid baroreceptors. Such stimulation results in an inhibition of the sympathetic nervous system (SNS), of the renin-angiotensin-aldosterone system, and of antidiuretic hormone (ADH, or arginine vasopressin, AVP). Diuresis and natriuresis and the resultant decrease in blood volume constitute the homeostatic response to such postural change.

Several studies have now documented a significant increase in the plasma norepinephrine (NE), plasma renin activity (PRA) and AVP in response to standing, upright tilt, or other orthostatic stress after bedrest (and presumably on return to Earth's 1-g). Individuals who do not show decreased orthostatic tolerance after bedrest show an increased NE, PRA, and AVP response — in contrast to those who do show orthostatic intolerance, where NE, PRA, and AVP response are not increased after bedrest. The endocrine system clearly underlies the ability to respond to orthostatic stress, not only by regulating blood volume but also by direct action on vascular smooth muscle and the kidney.

In addition, the hypothalamo-pituitary-adrenocortical responsiveness to orthostatic stress is similarly affected by bedrest and space flight. This system was among the first measured before and after the Mercury flights, which lasted from only 15 minutes to some hours. Throughout the various missions, data have indicated that space flight is indeed stressful, although weightlessness may in fact be a less stressful condition than

Earth's 1-g. For instance, although the cortisol rhythm remains reasonably stable, its amplitude and daily mean are lower indicating a lower total daily output. On the other hand, it is difficult to draw absolute conclusions since both flight and ground-based simulation (bedrest) measurements indicate that in the process of adapting to and attaining a new equilibrium in the absence of gravity, or with changes in the directional forces of gravity, the hypothalamo-pituitary-adrenal system appears to become unstable and decoupled. Evidence so far, however, has been indirect because classic tests of function have not been performed in either condition. Such a complete evaluation should be carried out, because this system is essential for the normal function and homeostasis of many essential body functions including reproduction, immunity, metabolism, and response to stress. The pituitary-adrenal system has also been shown to affect behavior and performance, often in different ways. In particular, more recent clinical work has emphasized the importance of the actions of CRF on the brain, not only in regulating the stress response but also in regulating mood and behavior, including food consumption and thirst. Similarly, thyroid stimulating hormone, like CRF has been found to have beneficial effects in seasonal, environmental depression.

Little unusual information has been obtained from flight or ground-based investigations regarding reproductive function. In short Shuttle missions, as in 7-day bedrest studies, female reproductive hormones and their cycles do not appear to be greatly affected. The effect of more prolonged exposures is completely unknown. On the other hand, animal data show decreases in testosterone after flight, but the significance of this is unclear. However, for prolonged missions, reproductive regulation and function should be addressed.

Finally, the interaction of endocrine regulatory system changes that occur as adaptive responses to microgravity must be considered in addressing how this altered regulatory baseline function may influence the response of other endocrine, non-endocrine, and behavioral and performance functions. Although we now believe that many of the known endocrine responses to space flight are adaptive responses to acute changes in hydrostatic pressures, there is no way of predicting from the data of the short missions achieved so far, what effect removal from the influence of millions of years of gravity would have during extended stays in microgravity.

4.3 CRITICAL QUESTIONS (In priority order)

1. What are the effects of space-induced endocrine changes on the function of other homeostatic systems (e.g. cardiovascular, central nervous system, immune function, thermoregulation, musculoskeletal system, gastrointestinal system, and energy metabolism)?
2. What are the hypothalamic-pituitary-adrenal and opioid system responses to normal space-flight events (e.g. EVA, countermeasures) as well as to reference "standardized" physical, emotional, and environmental stimuli?
3. What are the acute and chronic effects of space flight on endocrine system homeostasis and responsiveness?

4. How does space flight affect the pharmacodynamics of hormone action, the permeability of the blood-brain barrier, and the action and metabolism of hormones?
5. How do altered biological rhythms associated with long-term space flight affect hormone secretion and function and vice versa?
6. How does prolonged or repeated space flight affect regulation of mammalian reproductive cycles and behavior (including species, sex, and age differences)?

5.0 FLUID AND ELECTROLYTE REGULATION

5.1 INTRODUCTION

Regulation of body fluid and electrolyte balance is a fundamental homeostatic function of the body. Severe dehydration can be accompanied by circulatory collapse. Losses of electrolytes, especially sodium and potassium, can alter cardiac performance, thermal regulation, plasma osmolality, and cellular electrochemical gradients. To prevent these conditions from occurring, the body has developed feedback mechanisms that control both its fluid and electrolyte composition. Although the two functions are interdependent and share certain controls, some of the mechanisms controlling each are independent of the other. It should be noted that physiologists have, in general, concentrated their efforts on understanding the mechanisms controlling fluid and electrolyte losses. Much less effort has been spent in understanding the mechanisms controlling intakes of fluid and electrolytes.

The regulation of fluid and electrolyte balance is a fundamental homeostatic function of the body. It is important to understand as completely as possible the changes that occur during exposure to microgravity, as well as the changes that occur in the hormones and other factors regulating these balances. A more complete analysis of renal function is required to support the longer missions that will be involved with Space Station Freedom and beyond. Whether the changes in blood urea nitrogen that have been reported indicate changes in renal function should be investigated.

The mechanisms leading to the acute loss of fluid and electrolytes during the initial phase of adaptation to microgravity are not fully understood. Neither do scientists understand the mechanisms operative in the regulation and maintenance of fluid and electrolyte balance during the chronic phases of microgravity exposure. The magnitude, time course, and steady-state level of changes in key electrolytes and different body fluid compartments must be studied throughout the process of adaptation to microgravity. The functional relationship between changes in fluid and electrolyte regulatory mechanisms and cardiovascular system function and deconditioning during microgravity must be studied. Space Station Freedom will offer the opportunity to validate antiorthostatic bedrest as a method of simulating microgravity for studying long-duration space-flight-induced alterations in fluid and electrolyte metabolism.

5.2 BACKGROUND AND CURRENT KNOWLEDGE

It has been clear from the earliest manned space flights that exposure to microgravity is accompanied by a shift of fluids from the more peripheral (legs and feet) to the more cephalad part of the body. Puffiness of the face, reduction in the volume of the lower limbs, and other changes characteristic of this shift of fluid have been reported during exposure to microgravity. Similar changes in fluid distribution occur with horizontal and head-down bedrest.

The shift of fluid induces a net reduction in body fluids that contributes to a loss in body weight. The latter appears to be sustained throughout the period of exposure to microgravity and has been reported for virtually all space flights. The mechanisms responsible are not completely understood and may involve changes in the rate of secretion of a number of hormones, including aldosterone, catecholamines, atrial natriuretic hormone, antidiuretic hormone, and others. In addition, changes in renal hemodynamics (renal plasma flow) and glomerular filtration rate may contribute.

Toward the end of some U.S. and Soviet missions, fluids with salt have been prescribed to increase extracellular volume for the purpose of restoring orthostatic competence in preparation for return to 1 g. Except for partial repletion of water and salt shortly before re-entry, means of intervention to prevent fluid and electrolyte loss during the mission have not been identified. Furthermore, it is not clear whether such intervention is needed during the mission, since these changes may, in fact, be adaptive. If so, attempts to alter them could be counterproductive.

Decreases in the concentrations of sodium and potassium in serum, accompanied by an increase in the concentration of chloride, were reported after STS 1-4. Similarly, decreases in the concentration of sodium in serum were reported for the Apollo 8, 9, and 10 missions, while increases were observed for the Apollo 7 and 11 missions. Decreases in the concentration of potassium in serum were reported for the Apollo 7 and 8 missions, with an increase in the concentration of chloride in the Apollo 7 mission and a decrease in the Apollo 8 and 10 missions. An average decrease of 6.7 percent in exchangeable potassium occurred in astronauts of the Skylab 2, 3, and 4 missions. A decrease in the concentration of aldosterone in plasma was also reported after the STS 1-4 missions. In the latter missions, verification of the loss of sodium and potassium during exposure to microgravity was seen after return to 1 g, when retention of these electrolytes occurred in conjunction with an increase in the concentration of aldosterone in plasma.

Biomedical investigations associated with Skylabs 2, 3, and 4 identified a reduction in total body water from 1.1 to 4.5 percent during exposure to microgravity. An average reduction in extracellular fluid volume of about 2 percent occurred in the astronauts of these three missions. Plasma volume, measured before and after Gemini flights, was reduced by 13 percent after the 4-day flight, by 6 percent after the 8-day flight, and by 10 percent after the 14-day flight.

A brief review of the changes occurring in fluid and electrolytes during exposure to microgravity was published by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology in 1986. The major thrust of the review,

however, was in the area of nutrition. Several additional publications (see 6.0, Selected References) have also reviewed this area in greater depth.

Little direct information is available with respect to changes in renal function that may occur during exposure to microgravity. The early study of Lutwak and co-workers, carried out on the astronauts of Gemini VII, assumed that no changes occurred. Although no measures of renal clearance of any substances were made, increases in blood urea nitrogen (BUN) immediately after flight of 25 percent above preflight values in astronauts of STS 1-4 were reported. A similar increase was observed in astronauts from the Apollo 10 mission.

Thus, a question arises as to whether renal function may be impaired by exposure to microgravity. It has been postulated, based on the results of the Apollo missions, that a decrease in renal blood flow may have occurred. The nine crewmen in the Skylab program were in negative fluid balance during the first 6 days of flight. Reduced intake and an increase in insensible water loss (because of the low ambient humidity) are probably factors in the negative fluid balance. The possibility of potential changes in the mechanisms inducing thirst and drinking during exposure to microgravity has not been considered to date.

5.3 CRITICAL QUESTIONS (In priority order)

1. What are the time course and magnitude of fluid shifts and changes in fluid compartment volumes during acclimatization to hypogravity and during return to 1 g after flight?
2. What are the fluid and electrolyte regulating mechanisms underlying the cardiovascular responses to microgravity?
3. What are the mechanisms for the chronic adaptive shifts in fluid and electrolytes during space flight? How does the new steady state affect the body's ability to respond to heat stress, electrolyte loading, EVA, and countermeasures?
4. What are the effects of microgravity on renal function, e.g. stone risk and blood urea nitrogen? Are the effects progressive? Are they reversible? Are there differences in filtration, reabsorption, secretion, and excretion?
5. What are the best methods to accurately measure fluid loss, fluid intake, plasma volume, extracellular fluid, total body water, and interstitial volume in space flight?
6. What are the time course and magnitude of the diuresis, natriuresis, and kaliuresis resulting from exposure to hypogravity?
7. What are the mechanisms inducing the acute loss of fluid and electrolytes in microgravity?

8. What are the effects of circadian rhythm changes in space flight on the responsiveness of the fluid and electrolyte system?
9. What are the mechanisms regulating thirst and electrolyte appetite during space flight?
10. What are the roles of renal blood supply and renal electrolyte handling in extracellular fluid volume control during simulated and actual microgravity?
11. What are the relationships of fluid and electrolyte responses to space flight on sensory thresholds and space motion sickness?
12. What are the effects of pressure and gas composition in space flight and during EVA on changes on fluid and electrolyte regulation?
13. To what extent does the gastrointestinal system modify electrolyte and fluid balance control during space flight?

6.0 HEMATOLOGY

6.1 INTRODUCTION

Decreases in red blood cell mass and plasma volume have been observed consistently following manned space flights. Losses of red blood cell mass by U.S. astronauts have ranged from 2 to 21 percent. Based on postflight estimates of total hemoglobin, Soviet cosmonauts who have engaged in long-duration space missions have exhibited somewhat greater losses. Restoration of red blood cell mass appears to require from 4 to 6 weeks following return to Earth, regardless of the duration of space flight.

There are no reports suggesting that "astronaut anemia" has impaired the health and performance of members of space crews either during flight or after flight. Nevertheless, in-flight illnesses, injuries, or life support malfunctions could conceivably alter cardiovascular-respiratory requirements such that a 10 to 15 percent decrement in red blood cell mass could compromise crew safety and performance. Moreover, uncertainties exist as to the probable responses of the hematopoietic system during possible future space missions lasting a year or longer. Therefore, loss of red blood cell mass represents a contingent operational medical problem.

From the standpoint of the biologic effects of space flight, red blood cell mass loss is a significant, predictable response that may be a model of the effects of space flight on human proliferative tissues. Despite substantial investigation in the United States and Soviet Union, the etiology, biologic mechanisms, and potential operational significance of the loss of red blood cell mass has not been adequately defined. Authorities in space medicine, hematology, and related specialties regard this loss as one of the endpoints of physiologic adaptation to weightlessness. While the primary cause appears to be the influence of microgravity itself, the etiology is probably

multifactorial, including such influences as hypokinesis/hypodynamia, bone demineralization and remodeling, muscle atrophy, altered hemodynamics, and nutritional and metabolic disturbances. Other environmental influences such as hyperoxia, hypobaria, ionizing radiation, toxic contaminants, and accelerative stresses of space flight are probably not causal factors; however, their possible influence remains to be established.

Available information does not permit reliable extrapolation of the probable course of erythrokinetics during future space missions lasting a year or longer, nor can the possibility that red blood cell mass loss could compromise the safety and effectiveness of crewmembers be ruled out in flights complicated by illness, injury, or life support equipment malfunction.

A lack of sufficient information on several essential hematologic parameters emphasizes the need to expand data on red cell losses.

6.2 BACKGROUND AND CURRENT KNOWLEDGE

Red blood cell mass loss has been referred to as "astronaut anemia," "space anemia," or "anemia of space flight." Red blood cell mass losses of 2 to 21 percent are accompanied by decreases in hemoglobin mass (12-33 percent) and losses of 4-16 percent in plasma volume. Erythrocyte and hemoglobin concentrations in the blood remain constant, suggesting that losses in mass are related to a complex series of physiological responses to weightlessness, the most significant of which may be plasma volume loss. Evidence from prolonged flights by U.S.S.R. cosmonauts shows losses of hemoglobin mass without in-flight recovery from red blood cell mass losses. As with the results from U.S. studies of astronauts, postflight recovery is slow, taking up to 30 days or more.

Hematologic studies were conducted on four crewmembers on Spacelab 1 and six matched control subjects who served as a ground-based control group. As expected, hemoglobin concentration and hematocrit of the four Spacelab subjects increased 22 hours after exposure to weightlessness. On landing, hematocrit, red blood cell mass, plasma volume, and reticulocyte counts were reduced. However, while decreases in serum erythropoietin were noted in all flight crewmembers, the reductions in erythropoietin levels were not statistically significant. This lack of a significant reduction in serum erythropoietin levels accompanied by a significant decrease in reticulocyte number, together with the progressive loss of red blood cell mass during flight, suggests that inhibition of erythropoiesis was not the major or sole cause of red blood cell mass loss.

While there is no evidence that the reductions in red blood cell mass, in numbers of circulating reticulocytes, and in plasma volume affect performance adversely, their confirmed occurrence is viewed as an issue requiring investigation and explanation. The causes and mechanisms are poorly understood despite considerable investigation over the past several years. Although evidence is incomplete, most investigators consider the anemia of space flight to be an endpoint of the processes of adaptation to weightlessness. That is, it is a physiologic rather than a pathologic

response to microgravity and other aspects of space flight, just as polycythemia is a response to altitude.

While the number of in-flight animal studies has been limited, their results are significant in terms of factors causally related to red blood cell mass losses. Life-span of the red blood cells of male pathogen-free Wistar rats flown for 19.5 days in COSMOS-782 was reduced 5.4 percent and hemolysis of red blood cells was increased threefold when compared to control animals kept in a vivarium. In experiments with pathogen-free male Wistar rats flown on Cosmos-936 for 18.5 days, hemolysis of red blood cells was apparently related only to weightlessness because little or no hemolysis occurred in those rats that were centrifuged inflight to produce an artificial unit gravitational field.

Because bone marrow can compensate for reduced red blood cell life-span by increasing production of red blood cells, red blood cell mass might be expected to remain constant. But red blood cell mass decreased in rats held in the weightless condition not only because of hemolysis but also, probably, inhibition of erythropoiesis as illustrated by reduced hematopoietic responsiveness of marrow from space-flown rats.

6.3 CRITICAL QUESTIONS (In priority order)

1. Does the well documented decrease in red blood cell mass termed "anemia of space flight" represent a normal microgravity-associated adaptive process (self-limiting) or a transient response (self-correcting) to changes brought about by various space-flight-related stimuli (stressors)?
2. What are the time courses and magnitudes of changes in the erythropoietic system during space flight?
3. What is the most effective way to restore red cell mass during simulated and actual microgravity? Should red cell mass be restored during space flight?
4. Are these acute or chronic changes and are they of sufficient magnitude or duration to pose an unacceptable medical risk and warrant the development of countermeasures (prophylactic or therapeutic)?
5. What is the relationship between altered hematocrit, renal function, and erythropoietin levels in micro-, partial, and unit gravity?
6. What are the major factors and associated mechanisms that contribute to the "anemia of space flight"?
 - a. What controls the alterations in red cell production or survival?

- b. Does the loss of red cell mass result from an impairment of the red blood cell proliferation process or to differential margination, reticuloendothelial sequestration, cell death, or other mechanisms?
- 7. Is the "anemia of spaceflight" related to a direct effect of microgravity or other space-flight-induced stressors on bone marrow structure, function, or cellular interaction?
- 8. Are periods of recovery from "anemia of space flight" physiologically analogous to those in subjects who donate blood or otherwise undergo phlebotomy, and can this recovery be accelerated?

7.0 IMMUNOLOGY

7.1 INTRODUCTION

The immune system of higher animals is composed of the cells, tissues, and secretory products that allow the organism to discriminate "self" from "nonself" and to carry out the actions necessary to destroy and eliminate nonself entities from the body. Thus, the body is protected from exogenous (microbial) or endogenous (neoplastic) threats to survival. Besides the critical functions of monitoring the body's internal milieu for nonself molecules/organisms, such as bacteria, fungi, and viruses, the immune system plays an important "immune surveillance" role by identifying neoplastic or otherwise antigenically transformed cells and destroying them before they can form a tumor and/or metastasize. This latter function will be particularly important in a relatively high radiation environment or when crews are otherwise exposed to environmental toxicants (associated with space flight) that could increase the rate of mutation or tumorigenesis.

Because of the importance of its surveillance role in host defense, the organs and tissues of the immune system are widely distributed throughout the body (via blood and lymph). Both specific and nonspecific immunological functions are exhibited in higher animals.

Nonspecific immunity is a primary task of phagocytic cells (basophils, neutrophils, eosinophils, and macrophages) that form the body's first line of cellular defense. Specific immunity is functionally subdivided into "humoral" and "cell-mediated" systems. The effector cell in humoral immunity is the B-lymphocyte, which after encountering a foreign antigen or substance undergoes a series of cellular divisions (clonal expansion) to become a "plasma cell." The plasma cell produces millions of antibodies that are specifically targeted to the foreign substance that was initially encountered. The effector cells of the cell-mediated immune response are primarily the T-lymphocytes. In recent years, the important functions of a variety of immunoregulatory molecules (lymphokines, cytokines, enkephalins, etc.) secreted by accessory immune cells such as monocytes and macrophages, T and B cells themselves, and cells within the neuroendocrine system have been documented.

Studies to date, primarily on short-term space flights, suggest that changes in microbiological flora associated with long-term human habitation of closed environments include increases in antibiotic resistance; spread of normal skin flora to other body parts; increased interpersonal transfer of potential pathogens, "simplification" of species; growth to higher population densities, emergence of opportunistically pathogenic strains of bacteria and fungi; and loss of general (herd) immunity to bacterial, fungal, or viral strains present on/in newly arrived crewmembers. Any or all of these changes could be deleterious to human health, particularly if the humans were immunocompromised. The potential health risks associated with short-term flights (listed above) will probably be extended and increased with the advent of long-duration missions such as colonization of the Moon and Mars or other missions involving long-term human habitation of closed environments.

As the NASA manned space flight program readies itself for the challenges associated with maintaining human health and safety on long-duration flights, the question of the time course, magnitude, and potential clinical significance of changes in immune competency must be addressed with a program of clinical and scientific investigations involving carefully designed and integrated ground-based and in-flight studies. Any potential space-flight-related decrement(s) in immune function that would affect the identification and elimination of infectious organisms or surveillance of the internal environment for transformed cells must be identified rapidly, their potential impact on crew health and safety assessed, and, if required, appropriate prophylactic or therapeutic measures developed.

7.2 BACKGROUND AND CURRENT KNOWLEDGE

U.S. and Soviet biomedical researchers have been investigating the effects of space flight and microgravity on human immune function since the inception of manned space flight. However, the programs have been modest and the findings inconclusive. Although Skylab crews showed increased rates of gingivitis, postflight phytohemagglutinin (PHA) stimulation of lymphocytes taken from Skylab astronauts remained within preflight ranges (i.e. were not depressed). Postflight ribonucleic acid synthesis was reported to be decreased concomitant with an decrease in absolute leukocyte count.

The Soviets reported decreased tritiated uridine uptake in the lymphocytes of cosmonauts following the flights of Soyuz 6, 7, 8, and 9. Numerical measurements of lymphocytes and other leukocytes reported in these and other Soviet studies imply a transient postflight leukocytosis and lymphocytopenia. However the general theory that lymphocyte blast transformation is reduced in response to space flights was not supported by data from the flights of Soyuz 24, Salyut 5, Soyuz 26, Soyuz 27, or the Soyuz 28/Salyut 6 (98-day) mission. The Soviets reported increases in spontaneous lymphocyte activity and PHA-induced blastogenesis after these missions. Following the 140-day mission to Salyut 6, the Soviets again reported decreases in T lymphocyte number and impaired blast transformation.

Thus, at the beginning of the Space Shuttle Program, there were data suggesting that the in-vitro stimulability of lymphocytes was transiently depressed postflight, but much of the data were invalid or contradictory. Using an improved technique, it was later

demonstrated that the in-vitro blastogenic responsiveness of space crew peripheral blood lymphocytes was reduced by as much as 92 percent following short-duration Space Shuttle missions. Furthermore, data obtained from samples collected before and after 11 of the first 12 U.S. Space Shuttle flights generally show that absolute lymphocyte numbers, mitogen-induced blastogenesis, and circulating eosinophils are all transiently reduced after flight. Since these results are similar to functional changes exhibited by leukocytes from humans exposed to physical/emotional stress, a direct causal relationship to microgravity or other space-flight-unique stressors could not be established. Using monoclonal antibodies to surface antigens, flow cytometric analysis of lymphocytes taken from 11 crewmembers from STS-41B and STS-41D demonstrated a postflight decrease in circulating B lymphocytes and monocytes. Reduced PHA transformation correlated with the demonstrated lymphocytopenia and monocytopenia. Since monocytes are important accessories to T cell activation, through the action of cytokines, these findings suggest a mechanism for the postflight hyporeactivity of T cells to PHA.

In the area of cytokine/lymphokine research, interferon alpha/beta production has been studied in vitro using lymphocytes taken from four cosmonauts sampled pre- and postflight. However, the data were inconclusive.

In-vitro tests, stimulation of non-crewmember donor cells flown in space produced five times the levels of interferon alpha/beta as stimulation of ground controls. In the U.S., the antiorthostatic, hypodynamic, hypokinetic suspension of rodents in a 15-20 degree head-down posture (a model often used to simulate space-flight-induced changes in bone and muscle) resulted in an 80-percent suppression of interferon alpha/beta production. Decreased interferon production was also shown to correlate with enhanced susceptibility of rats to Encephalomyocarditis (EMC) virus. On Shuttle Spacelab-3 (SL-3), 9 of 10 test rats showed no measurable interferon production. Because of the importance of the roles that the interferons, interleukins, and other immunoregulatory molecules play in the immune response, future studies will elucidate the relationship between space flight and lymphokine/cytokine production.

The immunological studies flown on Cosmos biosatellites 1884 and 2044 were designed to test the efficacy of tail suspension as a model for microgravity-induced changes in immune function, the ability of bone marrow cells to respond to granulocyte/monocyte colony stimulating factor (GM-CSF) and the distribution of immunologically active cells after space flight as compared with 1-g controls. Results indicate that bone marrow cells from both flight and suspended rats had reduced capacities to respond to GM-CSF compared to cells from controls. A higher percentage of spleen cells from flown rats expressed T-helper and cytotoxic-suppressor T-cell markers than did those from controls; and, in the bone marrow, higher percentage of T-helper, suppressor-cytotoxic T, anti-asialo-GM-1-positive and IL-2 receptor-bearing lymphocytes were found in rats after space flight. Cells from tail-suspended rats, however, did not show these same increases. Therefore, tail suspension in 1-g does not induce the complete pattern of immunological changes associated with space flight.

7.3 CRITICAL QUESTIONS (In priority order)

1. Does space flight affect the humoral or cell-mediated immune functions, nonspecific immunity, or immune surveillance capabilities of space crews in a manner that would expose them to unacceptable medical risk while on a mission, upon return to Earth, or as a consequence of repeated mission exposure?
2. What are the time course and magnitude of space-flight-induced changes in the surface phenotypes (subpopulations), circulation patterns, or functional capacities of the cells of the immune system, including mucosal, humoral, cell-mediated and immune surveillance systems?
 - a. What factors cause or otherwise influence the consistently demonstrated post-flight reduction in blastogenic responsiveness to nonspecific mitogens (PHA, Con A, LPS)?
 - b. What are the dynamics of the leukocyte count during space flight with respect to:
 - induction of neutrophilia, lymphopenia, monocytopenia or eosinopenia
 - numbers and functional capacity of natural killer (NK) cells
 - other changes in the WBC differential count, or the circulation/sequestration of immunologically active cells?
3. Are there in-vitro tests that reliably predict decreases in immune function in space flight?
4. What is the prevalence and severity of infectious disease and carcinogenesis in crewmembers within 90 days of return from a mission — 1 year, 2 years, etc. (longitudinal study)? Does this prevalence suggest that space flight was a predisposing factor in disease incidence, severity, or delayed rate of recovery?
 - a. Does the length of flight or other mission characteristic affect the postflight recovery rate or acceptability of medical risk based on demonstrated changes in immune competency?
5. What are the relationships between the stressors associated with space flight; the source, duration and magnitude of the stressor; and decreased immune function?
 - a. Are there effective operational procedures or countermeasures to counteract the stressors or their effects?
6. Are there terrestrial (1 g) human, animal and/or computer models that simulate or reproduce the effects of space flight/microgravity with

sufficient validity that experimental results are reliable and predictive of immune responses in space?

7. What are the effects of space flight on the functional capacities of the effector/accessory cells of specific or nonspecific immunity (monocytes, neutrophils, macrophages, lymphocytes, and NK cells)?
8. Do any of the changes in the immune system predispose crewmembers either during or after flight to infectious diseases, allergies, or delays in recovery from disease or wound healing?
9. How long do neutrophilia, lymphocytopenia, monocytopenia, eosinopenia, and reduced blastogenic responses persist after flight?
10. Are there other in-vitro/biochemical assays that reliably predict or reflect decreases in immune function and if added to the current battery of postflight tests, would give a more complete picture of factors affecting immune function?

8.0 METABOLISM AND NUTRITION

8.1 INTRODUCTION

The metabolic status and nutritional requirements of human beings are known to be affected by changes in physiological states. The major biologic effects associated with the weightless environment of space flight include bone demineralization, cardiovascular deconditioning, muscle atrophy, body fluid changes, and neurophysiological dysfunctions. These physiological responses to weightlessness, as well as the limited food choices, and exposure to radiation during space flight, can all potentially affect human metabolism and nutritional requirements, which in turn affect physiological systems. Thus, metabolic regulation and nutritional balance are integral parts of maintaining astronauts' health and performance in space.

During acute and long-term exposure to microgravity, the metabolic needs and energy requirements of individuals may change relative to their requirements on the ground. Therefore, human metabolic efficiency and steady-state energy expenditure in space during nominal activities, exercise, and extravehicular activities should be determined. If there are changes, key physiological factors underlying the differences must be elucidated.

The physiologic changes for which countermeasures are being considered include bone demineralization, muscle atrophy, body fluid shifts, and electrolyte imbalances. All of these changes can be affected by an individual's metabolic and nutritional status; therefore, nutritional countermeasures are believed to be an integral part of other countermeasure programs. In-flight exercise, for example, is considered a primary countermeasure against muscle atrophy, and, with appropriate weight loading, may also be useful in minimizing bone demineralization. Provision of

adequate protein or special amino-acid combinations may aid in preventing muscle atrophy.

The therapeutic effect of any drug is dependent upon the rate at which it is absorbed, metabolized, and eliminated, as well as its volume of distribution within the body. Changes in gastrointestinal, hepatic, or renal function or in circulatory dynamics may modify the pharmacodynamics of a number of drugs and the function of the gastrointestinal tract, liver, and kidneys during space flight should be established.

8.2 BACKGROUND AND CURRENT KNOWLEDGE

With the exception of energy, no nutritional requirements have been evaluated as yet for living in space. The nutrients provided to meet the metabolic needs of astronauts have been considered adequate for space flights of short duration. However, with the 90-day tours projected for the Space Station Freedom, nutritional and metabolic studies are essential. Energy deficits and body weight losses that were sustained on short missions may not be tolerated on missions of long duration.

During the early space missions, it was assumed that fewer calories would be required in space than on Earth because of the reduced muscular load in a weightless environment. This assumption has been proven incorrect. Experience gained from longer flights, during which loss of body weight was significant, led to increasing the total energy content of the space diet from 2500 kcal/day to about 3000 kcal/day. In an effort to meet energy demands for sustained performance, the proportions of protein, fat, and carbohydrate were adjusted to provide more protein and carbohydrate and less fat. In-flight weight losses have not been abolished. The physical condition of astronauts seems to improve when increased caloric intake was accompanied by an elevated level of exercise. On the longer Soviet space flights, the total energy content of the diet and both the intensity and variety of the exercise program have been progressively increased.

In addition, on early space missions, dietary palatability was low, and the intended quantities were not always consumed. However, in the Shuttle program, the variety of foods and dispensing techniques has been increased and palatability improved. Because storage has been a problem in terms of weight and bulk, dehydrated and thermostabilized foods that could be reconstituted aboard the spacecraft have been preferred by NASA. In an effort to provide a diet meeting the necessary requirements for calories, electrolytes, and nutrients compatible with metabolic balance, a standardized menu that accommodated individual food preferences was designed.

In order to provide protocols for Space Station Freedom, the methodologies associated with nutritional and metabolic requirements for long-duration flight should be tested on Shuttle missions, and operational data should be obtained for evaluation and possible extrapolation to long-term flights.

Soviet scientists have observed changes in some biochemical indices of GI function in rats exposed to microgravity, in subjects undergoing experimental bedrest, and in cosmonauts after space missions. Alterations in GI function will become more important with longer missions, since the GI tract directly influences absorption of

nutrients and fluids as well as orally administered drugs. GI function is currently being evaluated in bedrest subjects using techniques to estimate rates of gastric emptying and GI motility. Pilot studies suggest that GI function is indeed altered during bedrest. Further, the pharmacokinetics of scopolamine were studied in subjects undergoing antiorthostatic (6 degrees head-down) bedrest after intravenous or oral administration, and its bioavailability was found to decrease significantly during the bedrest period. The pharmacokinetics of orally administered acetaminophen and scopolamine/dextroamphetamine was evaluated during brief Shuttle flights, and preliminary pre- to in-flight comparisons indicate changes in drug-concentration profiles. Therefore, alternatives to oral administration (i.e. parenteral routes) may be more appropriate for treating disorders, such as space motion sickness, that have a GI component. During flight, differences during the absorption phase are more pronounced than those during the elimination phase. These limited in-flight data are inadequate to characterize the degree, magnitude, or mechanisms underlying space-flight-induced pharmacokinetic changes. They do, however, suggest that drug efficacy may differ in space, and allow identification of some of the variables that may influence disposition profiles. This information can also be applied to identifying and characterizing alterations in key processes within the body that are relevant to overall metabolic homeostasis in humans.

Increase in glycogen deposition has been noted after flight in rodents' muscle and liver, indicating that the control of intermediary metabolism is modified during space flight.

Research efforts can be grouped roughly into: quantifying energy requirements in space; evaluating methods of body-composition analysis; quantifying nutrient and micronutrient content of astronauts' diet; examining drug pharmacodynamics (both generally and for specific drugs); and developing countermeasures. It should be noted that, historically, data concerning nutrition and human metabolism, whether before, during, or after flight, have been difficult to obtain; careful advanced planning for obtaining such data from crews who remain in space for 3 months will be required.

8.3 CRITICAL QUESTIONS (In priority order)

1. Does space flight alter the energy requirements of humans, in particular, the minimum and nominal energy requirements? How do these requirements change during long-term acclimatization to space flight? Is the basal metabolic rate and metabolic efficiency altered during extended space flight? Are there changes in energy metabolism and storage in space, especially in substrate utilization?
2. What are crew food consumption patterns during space flight? What are the effect of changes in cell and nutrient turnover during space flight on nutritional requirements? What are the optimal noninvasive microanalytical methods and techniques for use during space flight to monitor nutritional status?
3. What are the mechanisms underlying the negative nitrogen balance and changes in lean body mass incurred during space flight? What are

possible interventions, including dietary alterations in proteins and amino acids?

4. What are the pharmacokinetics (absorption, distribution, metabolism, and elimination) of drugs likely to be used in space? Which methods of administering drugs are the most effective in providing a predictable response during space flight?
5. Do the effects of space flight require added supplements of vitamins, minerals, or other nutrients? What is the safe range of exogenous vitamin intake for long-term space flight? Are nutritional requirements modified by transient digestive disturbances, such as the anorexia, nausea, and vomiting associated with space sickness?
6. What are the energy requirements of EVA? What are the effects of deconditioning, EVA, and countermeasures on nutritional requirements and body composition during space flight?
7. Are there valid ground models and analogs for the study of the effects of space flight on nutrition?
8. What is the time course and nature of body composition change due to space flight? Do changes in body composition (age and gender) have an effect on crew health and performance?
9. What is the optimal presentation, nutritional and caloric formulation of the diet for maintaining crew health and performance in space flight? What are the behavioral and performance responses of individuals to particular food constituents during space flight? Are there changes in dietary preference?
10. Is there a change with respect to "food allergies" or other abnormal reactions to foodstuffs? Is there an accumulation of heavy metals and/or other toxic metals or compounds during long-term bedrest or space flight?
11. Does space flight alter gastrointestinal physiology, including the absorption of essential nutrients and the functioning of gut flora? What are the effects of space flight on liver function? Are the effects progressive? Are they reversible?
12. What are the effects of space-flight-related factors, (e.g. bone demineralization and light spectrum) on nutritional requirements?
13. What changes in carbohydrate/lipid metabolism occur during space flight? Are they modified by dietary intake?

9.0 TEMPERATURE REGULATION

9.1 INTRODUCTION

Temperature regulation in mammals is an example of a highly complex regulatory system maintaining homeostatic conditions in the face of wide variation in environmental conditions. Temperature regulation in mammals has been extensively studied from pharmacological, physiological, psychological, neurobiological, and anatomical standpoints. Thermoregulation involves a continuum of neural structures including the limbic system, lower brainstem, reticular formation, spinal cord, sympathetic ganglia, and the hypothalamus. Gordon and Heath (see 6.0, Selected References) have summarized the current view on effectors controlled by this continuum. Other than sweat glands and brown adipose tissue, no specific organs have been identified as being used primarily by the thermoregulatory system. Rather, temperature regulation has evolved through the utilization of pre-existing physiological systems, e.g. the locomotor system for shivering, cardiovascular system for temperature control, and respiratory system for evaporative heat loss. Many neural studies on the control of effectors are motivated by an interest in the complexity of the system and an interest in describing neural activity, particularly in the hypothalamus, a key site for the integration of sensory signals to provide appropriate efferent controlling signals.

In man, except for an occasional episode of fever or exercise-induced hyperthermia, body temperature rarely varies more than 2 degrees C about baseline throughout an individual's lifetime. A normally functioning thermoregulatory system is vital for the health of the individual. For example, thermoregulation is drastically impaired by the alterations in body fluids that can occur during dehydration. Sustained high fever can be damaging. Moreover, numerous epidemiological studies have documented the adverse effects of low ambient temperatures on elderly individuals. Even transient exposure to high temperatures leads to discomfort and radically impairs sleep and performance.

Alterations in core temperatures have been observed during space flight and have attracted attention to the thermoregulatory system as a system that is modified by exposure to a microgravity environment. These observations on COSMOS and Spacelab flights have led to numerous NASA-supported studies on this regulatory system in a hypergravic environment, so that at this time a description of thermoregulation as a function of gravity is beginning to emerge. Further information is needed to more completely detail thermoregulatory mechanisms, especially in a partial-g or microgravity environment, as this system is important for optimal function of humans in space.

Examples of NASA analyses with regard to temperature regulation are those in the 1988 report entitled, NASA Workshop on Biological Adaptation. This report briefly reviews studies in hypergravic and microgravity environments, and concludes by stating that remaining basic areas that merit further investigation include determining in more detail how gravity influences temperature regulation.

With further information on the interaction of ambient temperature and the effects of altered gravitational fields (e.g. fluid shifts) on comfort and performance of humans in space, more exact engineering specifications for spacecraft design can be established.

9.2 BACKGROUND AND CURRENT KNOWLEDGE

While there have been relatively few experiments conducted in space on temperature regulation in mammals, there is convincing evidence that temperature regulation is altered in space flight. During the flight of COSMOS 1514, body temperature of a monkey was monitored via biotelemetry implants. Microgravity appeared to alter the steady-state regulation of body temperature, since over the course of the 5-day flight there was a reduction in core temperature. The circadian rhythm was maintained but the phase and/or period were altered. Similar observations were made in rats flown on Spacelab 3. Such alterations were not observed in heart rate or activity. These observations support the hypothesis that at least two neural oscillators are involved in the generation of circadian rhythms and, furthermore, suggest that the temperature oscillator is gravity sensitive. Informal discussions with Soviet scientists have revealed that cosmonauts are at times cold and require extra clothing, indicating modified temperature regulation in space. All these observations are provocative, but further experiments are needed to provide more detailed information on the nature of thermoregulatory deficits in microgravity. It seems that the thermoregulatory system functions optimally at 1 g and that core temperature is, at least initially, reset to a lower level in microgravity.

Utilizing animal centrifuges, temperature regulation has been extensively studied in hypergravic fields. Oyama and his colleagues in 1971 were the first to show that rats exposed to a hypergravic field displayed a marked fall in core temperature, T_C . This fall in T_C was followed by several hours of relatively constant, although low, body temperature and then by a slow return toward normal levels over a period of several days. This observation in rats has been verified by many studies in other laboratories, and it formed the basis for more detailed investigations on altered neural control leading to impaired activation of thermogenic effectors. The fall in T_C on exposure to hypergravic fields has also been observed in dogs and monkeys. The numerous studies of temperature regulation in hypergravic fields all point toward an impairment of temperature regulation proportional to the intensity of the gravitational field. These space-related research projects have further elucidated the nature of alterations encountered in hypergravic fields.

9.3 CRITICAL QUESTIONS (In priority order)

1. What are the effects of space flight on thermoregulation processes and heat exchange?
2. What are the compounded effects of microgravity and EVA on thermoregulatory processes and heat exchange?
3. What environmental conditions of space flight influence temperature regulation?

4. What are the effects of prescribed countermeasures on thermoregulation?
5. How does the regulation of body temperature change during space flight? How do these changes affect the response to thermal load?
6. How are changes in body temperature or its regulation correlated with metabolic rate and energy expenditure?
7. How does space flight affect central and/or peripheral thermoregulatory mechanisms?

10.0 TECHNOLOGY

The most critical requirements for in-flight research in regulatory physiology are refrigerator freezers and blood and urine collection systems.

The development of an in-flight centrifuge for the generation of gravitational fields other than microgravity in space flight would provide capabilities for 1-g fields for in-flight controls and other 1-g studies; fractional g for threshold and planetary simulation studies; hyper-g (1-2 g) for provocative testing; and artificial gravity studies. At a minimum, this technology should be available for acute and chronic animal studies, particularly using non-human primates. Human-rated facilities will be required if artificial gravity fields are to be used as a countermeasure for crews in long-duration stays in space.

Other technology requirements are driven by the need for ground-based and in-flight techniques and sensors for measuring physiological information or sampling and storing/analyzing biological specimens of interest. Sensors, and their mode of attachment, must be of minimal impact on the subjects and capable of recording accurate information for extended periods of time. Animal housing requirements will necessitate the use of unrestrained animals in the future. In view of the fact that many physiological and behavioral processes (e.g. almost all hormones, body temperature, sleep, and performance) show pronounced fluctuations in time (both ultradian and circadian in nature) over the course of the day, a complete understanding of how microgravity affects these systems requires frequent in-flight sampling of the variable in question. As such, advances in the state of implantable multichannel biotelemetry systems and other noninvasive technologies will be required.

Biosample collections (e.g. blood, urine, feces, or biopsies) should also be made at frequent intervals for accurate interpretation of the data. Techniques will be required for taking frequent samples over extended periods of time. Moreover, collection and analysis procedures should be microminiaturized both to protect the subject (human or animal) and reduce the requirements for storage of material.

The continuous nature of the data collection in this discipline requires the ability to collect and store large amounts of data. This is particularly true for sleep or other

biopotential data. Thus, the development of intelligent data systems that are small (can be worn by the crew or integrated into the animal habitats), capable of recording from multiple channels, sampling at high frequencies, and have sufficient storage capacity (possibly preprocessing the data to reduce this requirement) is required.

The planning for long-duration exploration missions requires an understanding in as much detail as possible of the effects of prolonged exposure to microgravity on the critical physiological systems of the body. All protocols for experiments in space that propose to use single-point measurements for variables that show pronounced ultradian and/or circadian variations should be examined to ensure that data, which will be collected at enormous cost, are valid and meaningful. Therefore, efforts should be made towards the standardization of techniques for the collection, processing, and analysis of data/samples. Furthermore, any advances that can be applied to advanced methodologies to simplify assay procedures in space will reduce biospecimen sampling and storage requirements, reducing crew time and storage space — two major impacts of life sciences on space research.

11.0 RESEARCH STRATEGY

11.1 APPENDIX

The Regulatory Physiology research area priorities for each of the NASA mission eras are presented in Table 1.

Table 1
RANKINGS OF RESEARCH AREA PRIORITIES

REGULATORY PHYSIOLOGY	STS ERA CURRENT 1992-1995	SPACE STATION ERA 1991-2000	SPACE EXPLORATION ERA 2000-3000
RHYTHMS	1	1	2.5
ENDOCRINOLOGY	2	3	4.5
HEMATOLOGY	4.5	7	6
IMMUNOLOGY	4.5	3	2.5
METABOLISM/ NUTRITION	6	3	1
FLUID & ELECTROLYTES	3	5	4.5
TEMPERATURE	7	6	7

11.2 EXPERIMENTAL MODELS

11.2.1 Biological Models

The combined use of human, animal, and organ/tissue/cell culture models for experimentation will be essential for the understanding of the effects of space flight on the regulatory physiology systems. While the major questions to be addressed are often the same in animal and human studies, only human subjects will be appropriate for certain studies, such as group social interactions, and psychological and scheduling-related issues. Conversely, animal models will be required for other studies that require precise control of the environment (particularly in space-flight studies), variable gravity research (via centrifugation), and invasive preparations considered inappropriate for humans. In addition, data obtained from animals will be important for the design and interpretation of concurrent and follow-on studies in humans.

Of particular note here is the use of nonhuman primate models for biomedical research. Primates, such as the rhesus macaque or squirrel monkey, have been repeatedly demonstrated morphological, behavioral, and physiological similarities with humans. This knowledge combined with the ability to study these animals using invasive techniques in precisely controlled environments makes them powerful models for the study of human biomedical problems. The utilization of these models in long-term space studies will be a critical component of this Discipline Science Plan.

In addition to the space environment, space flight presents a number of special stressors for the human crew. These include: (1) small group confinement for extended periods, (2) a hazardous environment requiring ground-based support, and (3) rigorous operational demands. While animal experiments can be expected to provide insights and information about the response of mammals to space, many of the issues raised above can only be addressed appropriately in humans.

11.2.2 Ground-Based Analogs

These studies should focus on the individual effects of the various environmental changes associated with space flight. Human as well as various animal models will be required for such a program. Minimally, this program should include the use of both nonhuman primates and rodents. Of particular importance is the development of experimental situations that can isolate the specific effects of changes in the gravitational field on these various physiological systems.

The focus of ground-based studies should be on those issues that relate specifically to future human voyages into space. The emphasis should be on the characterization of the fundamental properties of these physiological systems in the space environment. These include the effects of gravity and other space-related factors (e.g. radiation, atmosphere, etc.) on the homeostatic and adaptive mechanisms of these systems. The effects of gender and age on these parameters also should be considered.

The types of analog models to be considered should include:

1. Centrifugation
 - Hypergravity
 - 1-g in-flight controls
 - Fractional g
2. Antiorthostasis, hypodynamia, and hypokinesia
 - Bedrest
 - Suspension models
3. Closed operational environments
 - Polar
 - Submarine
 - Hyperbaric

11.2.3 Mathematical Simulation

Mathematical models of physiological systems have been established in many of these subdisciplines. The modeling approach is of interest to basic science because it allows one to generate testable hypotheses, as well as testing the model itself. Models also have considerable practical implications and modeling can lead to new insight into the relevance of data obtained in animals to humans. Once established, modeling can reduce the level of empirical testing necessary on biological subjects.

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PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights ^a (1-14 days)	Long-Term Space Flights (more than 2 weeks) ^b	
		Pre- vs. Inflight	Pre- vs. Postflight
Cardiopulmonary System			
Heart rate (resting)	Slight increase inflight. Increased post-flight; peaks during launch and reentry, normal or slightly increased during mission. RPB ^c : up to one week.	Normal or slightly increased.	Increased. RPB ^c : 3 weeks.
Blood pressure (resting)	Normal; decreased postflight.	Diastolic blood pressure reduced.	Decreased mean arterial pressure.
Orthostatic tolerance	Decreased after flights longer than 5 hours. Exaggerated cardiovascular responses to tilt test, stand test, and LBNP postflight. RPB ^c : 3-14 days.	Highly exaggerated cardiovascular responses to inflight LBNP (especially during first 2 weeks), sometimes resulting in presyncope. Last inflight test comparable to R + O ^a (recovery day) test.	Exaggerated cardiovascular responses to LBNP. RPB ^c : up to 3 weeks.
Cardiac size	Normal or slightly decreased cardio/thoracic ratio (C/T) postflight.		C/T ratio decreased postflight.
Stroke volume	Increased the first 24 hours inflight, then decreased by 15%.	Same as short duration missions.	12% decrease on average.
Left end diastolic volume	Same as stroke volume.	Same as short duration missions.	16% decrease on average.
Cardiac output	Unchanged.	Unchanged.	Variable RPB ^c : 3-4 weeks.
Central venous pressure (indirect measurement)	Gradual decrease over 7 days inflight.	Not measured.	Not measured.
Left cardiac muscle mass thickness	Unchanged.	Unchanged.	11% decrease, return to normal after 3 weeks.
Cardiac electrical activity (ECG/VCG)	Moderate rightward shift in QRS and T postflight.	Increased PR interval, QT _c interval, and QRS vector magnitude.	Slight increase in QRS duration and magnitude; increase in PR interval duration.
Arrhythmias	Usually premature atrial and ventricular beats (PABs, PVBs). Isolated cases of nodal tachycardia, ectopic beats, and supraventricular bigeminy inflight.	PVBs and occasional PABs; sinus or nodal arrhythmia at release of LBNP inflight.	Occasional unifocal PABs and PVBs.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights* (1-14 days)	Long-Term Space Flights (more than 2 weeks) ^b	
		Pre- vs. Inflight	Pre- vs. Postflight
Systolic time intervals	Not measured.	Not measured.	Increase in resting and LBNP-stressed PEP/ET Ratio. RPB: 2 weeks.
Exercise capacity	No change or decreased postflight; increased HR for same O ₂ consumption; no change in efficiency. RPB: 3-8 days.	Submaximal exercise capacity unchanged.	Decreased postflight, recovery time inversely related to amount of inflight exercise, rather than mission duration.
Lung volume	Not measured.	Vital capacity decreased 10%.	No change.
Leg volume	Decreased up to 3% postflight. Inflight, leg volume decreases exponentially during first 24 hours, and plateaus within 3 to 5 days.	Same as short missions.	15% decrease in calf circumference.
Leg blood flow	Not measured.	Marked increase.	Normal or slightly increased.
Venous compliance in legs	Not measured.	Increased: continues to increase for 10 days or more; slow decrease later inflight.	Normal or slightly increased.
Body Fluids			
Total body water	3% decrease inflight.		Decreased postflight.
Plasma volume	Decreased postflight (except Gemini 7 and 8).		Markedly decreased postflight. RPB: 2 weeks increased at R + 0; decreased R + 2 (hydration effect).
Hematocrit	Slightly increased postflight.		
Hemoglobin	Normal or slightly increased postflight.	Increased first inflight sample; slowly declines later inflight.	Decreased postflight RPB: 1-2 months.
Red blood cell (RBC) mass	Decreased postflight; RPB: at least 2 weeks.	Decreased ~15% during first 2-3 weeks inflight; begins to recover after about 60 days; recovery of RBC mass is independent of the stay time in space.	Decreased postflight RPB: 2 weeks to 3 months following landing.
Red cell half-life (⁵¹ Cr)	No change.		No change.

Iron turnover			
Mean corpuscular volume (MCV)	Increased postflight; RPB: at least 2 weeks.		No change. Variable, but within normal limits.
Mean corpuscular hemoglobin (MCH)	Increased postflight; RPB: 2 weeks.		Variable, but within normal limits.
Mean corpuscular hemoglobin concentration (MCHC)	Increased postflight; RPB: at least 2 weeks.		Variable, but within normal limits.
Reticulocytes	Decreased postflight; RPB: 1 week.		Decreased postflight. In Skylab, RPB: 2-3 weeks for 28-day mission, 1 week for 59-day mission, and 1 day for 84-day mission.
White blood cells	Increased postflight, especially neutrophils; lymphocytes decreased; RPB: 1-2 days. No significant changes in the T/B lymphocyte ratios.		Increased, especially neutrophils; postflight reduction in number of T-cells and reduced T-cell function as measured by PHA* responsiveness; RPB: 3-7 days; transient postflight elevation in B-cells; RPB: 3 days.
Red blood cell morphology	No significant changes observed postflight.	Increase in percentage of echinocytes; decrease in discocytes.	Rapid reversal of inflight changes in distribution of red cell shapes; significantly increased potassium influx; RPB: 3 days.
Plasma proteins	Occasional postflight elevations in α_2 -globulin, due to increases of haptoglobin, ceruloplasmin, and α_2 -Macroglobulin; elevated IgA and C ₃ factor.		No significant changes.
Red cell enzymes	No consistent postflight changes.	Decrease in phosphofructokinase; no evidence of lipid peroxidation and red blood cell damage.	No consistent postflight changes.
Serum/plasma electrolytes	Decreased K and Mg postflight.	Decreased Na, Cl, and osmolality; slight increase in K and PO ₄ .	Postflight decreases in Na, K, Cl, Mg; Increase in PO ₄ and osmolality.
Serum/plasma hormones	Inflight increases in ADH, ANF, and decreases in ACTH, aldosterone and cortisol. Inflight decrease in glucose.	Increases in cortisol. Decreases in ACTH, insulin.	Postflight increases in angiotensin, aldosterone, thyroxine, TSH and GH; decrease in ACTH.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights* (1-14 days)	Long-Term Space Flights (more than 2 weeks) ^b	
		Pre- vs. Inflight	Pre- vs. Postflight
Serum / plasma metabolites & enzymes	Postflight increases in blood urea nitrogen, creatinine, and glucose; decreases in lactic acid dehydrogenase, creatinine phosphokinase, albumin, triglycerides, cholesterol, and uric acid.		Postflight decrease in cholesterol, uric acid.
Urine volume	Decreased postflight.	Decreased early inflight.	Decreased postflight.
Urine electrolytes	Postflight increases in Ca, creatinine, PO ₄ , and osmolality. Decreases in Na, K, Cl, Mg.	Increased osmolality, Na, K, Cl, Mg, Ca, PO ₄ . Decrease in uric acid excretion.	Increase in Ca excretion; initial postflight decreases in Na, K, Cl, Mg, PO ₄ , uric acid; Na and Cl excretion increased in 2nd and 3rd week postflight.
Urinary hormones	Inflight decreases in 17-OH-corticosteroids, increase in aldosterone; postflight increases in cortisol, aldosterone, ADH, and pregnanediol; decreases in epinephrine, 17-OH-corticosteroids, androstosterone, and etiocholanolone.	Inflight increases in cortisol, aldosterone, and total 17-ketosteroids; decrease in ADH.	Increase in cortisol, aldosterone, nor-epinephrine; decrease in total 17-OH-corticosteroids, ADH.
Urinary amino acids	Postflight increases in taurine and β -alanine; decreases in glycine, alanine, and tyrosine.	Increased inflight.	Increased postflight.
Sensory Systems			
Audition	No change in thresholds postflight.		No change in thresholds postflight.
Gustation & olfaction	Subjective and varied human experience. No impairments noted.	Same as shorter missions.	Same as shorter missions.
Somatosensory	Subjective and varied human experience. No impairments noted.	Subjective experiences (e.g., tingling of feet).	

Vision	Transitory postflight decrease in intraocular tension; postflight decreases in visual field; constriction of blood vessels in retina observed postflight; dark adapted crews reported light flashes with eyes open or closed; possible postflight changes in color vision. Decrease in visual motor task performance and contrast discrimination. No change in inflight contrast discrimination, or distant and near visual acuity.	Light flashes reported by dark adapted subjects frequency related to latitude (highest in South Atlantic Anomaly, lowest over poles).	No significant changes except for transient decreases in intraocular pressures.
Vestibular system	40-50% of astronauts / cosmonauts exhibit inflight neurovestibular effects including immediate reflex motor responses (postural illusions, sensations of tumbling or rotation, nystagmus, dizziness, vertigo) and space motion sickness (pallor, cold sweating, nausea, vomiting). Motion sickness symptoms appear early in-flight, and subside or disappear in 2-7 days. Postflight difficulties in postural equilibrium with eyes closed, or other vestibular disturbances.	Inflight vestibular disturbances are same as for shorter missions; markedly decreased susceptibility to provocative motion stimuli (cross-coupled angular acceleration) after 2-7 days adaptation period. Cosmonauts have reported occasional reappearance of illusions during long-duration missions.	Immunity to provocative motion continues for several days postflight. Marked postflight disturbances in postural equilibrium with eyes closed. Some cosmonauts exhibited additional vestibular disturbances post-flight, including dizziness, nausea, and vomiting.
Musculoskeletal system			
Height	Slight increase during first week inflight (~1.3 cm). RPB: 1 day.	Increased during first 2 weeks inflight (maximum 3-8 cm); stabilizes thereafter.	Height returns to normal on R + 0.
Mass	Postflight weight losses, average about 3.4%; about 2/3 of the loss is due to water loss, the remainder due to loss of lean body mass and fat.	Inflight weight losses average 3-4% during first 5 days; thereafter, weight gradually declines for the remainder of the mission. Early inflight losses are probably mainly due to loss of fluids; later losses are metabolic.	Rapid weight gain during first 5 days postflight, mainly due to replenishment of fluids. Slower weight gain from R + 5** to R + 2 or 3 weeks. Amount of postflight weight loss is inversely related to inflight caloric intake.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH SHORT-TERM AND LONG-TERM SPACE FLIGHT

Physiological Parameter	Short-Term Space Flights* (1-14 days)	Long-Term Space Flights (more than 2 weeks) ^b	
		Pre- vs. Inflight	Pre- vs. Postflight
Body composition		<p>Fat is probably replacing muscle tissue. Muscle mass, depending on exercise regimens, is partially preserved.</p>	
Total body volume	Decreased postflight.	Center of mass shifts headward.	Decreased postflight.
Limb volume	<p>Inflight leg volume decreases exponentially during first mission day; thereafter, rate of decrease declines until reaching a plateau within 3-5 days.</p> <p>Postflight decrements in leg volume up to 3%; rapid increase immediately postflight, followed by slower RPB.</p> <p>Decreased inflight and postflight; RPB: 1-2 weeks.</p>	<p>Early inflight period same as short missions. Leg volume may continue to decrease slightly throughout mission. Arm volume decreases slightly.</p>	<p>Rapid increase in leg volume immediately postflight, followed by slower RPB.</p>
Muscle strength			<p>Postflight decrease in leg muscle strength, particularly extensors. Increased use of inflight exercise appears to reduce postflight strength losses, regardless of mission duration. Arm strength is normal or slightly decreased postflight.</p> <p>Postflight EMGs from gastrocnemius show shift to higher frequencies, suggesting deterioration of muscle tissue; EMGs indicate increased susceptibility to fatigue. RPB: about 4 days.</p>
EMG analysis	<p>Postflight EMGs from gastrocnemius suggest increased susceptibility to fatigue and reduced muscular efficiency. EMGs from arm muscles show no change.</p>		<p>Reflex duration decreased postflight (by 30% or more). Reflex magnitude increased. Compensatory increase in reflex duration about 2 weeks postflight; RPB: about 1 month.</p>
Reflexes (Achilles tendon)	Reflex duration decreased postflight.		

Nitrogen & phosphorus balance		Negative balances early in flight; less negative or slightly positive balances later in flight.	Rapid return to markedly positive balances postflight.
Bone density	Os calcis density decreased postflight. Radius and ulna show variable changes, depending upon method used to measure density.		Os calcis density decreased postflight; amount of loss is correlated with mission duration. Little or no loss from non-weightbearing bones. RPB is gradual; recovery time is about the same as mission duration.
Calcium balance	Increasing negative calcium balance in flight.	Excretion of Ca in urine increases during 1st month in flight, then plateaus. Fecal Ca excretion declines until day 10, then increases continually throughout flight. Ca balance is positive preflight, becoming increasingly negative throughout flight.	Urine Ca content drops below preflight baselines by day 10; fecal Ca content declines, but does not reach preflight baseline by day 20. Markedly negative Ca balance postflight, becoming much less negative by day 10. Ca balance still slightly negative on day 20. RPB: at least several weeks.

* Compiled from biomedical data collected during the following space programs: Mercury, Gemini, Apollo, ASTP, Vostok, Soyuz and Shuttle Spacelab.

^b Compiled from biomedical data collected during Skylab and Salyut missions.

^c RPB: Return to preflight baseline.